REMARKS

Claims 1, 26, 28, and 53 are pending in the present application.

Claims 2-25, 27, and 29-52 have been canceled without prejudice.

Claim 1 has been amended to delete the term "human" and to specify that the attenuated *Salmonella typhimurium* vector comprises an aroA $^-$, dam $^-$ *Salmonella typhimurium* strain. Support for these amendments can be found in the specification, e.g., at pg. 20, lines 16-17.

No new matter is added by these amendments.

Rejections Under the Second Paragraph of 35 U.S.C. §112.

Claims 1, 26 and 53 stand rejected as allegedly being indefinite because the claim recited the phrase "human survivin protein" whereas SEQ ID NO: 3, recited in claims 26 and 53, is mouse survivin (the elected species). In response the word human has been deleted from claim 1.

Rejections Under 35 U.S.C. §103(a).

Claim 1 stands rejected as allegedly being obvious under 35 U.S.C. §103(a) over the combination of Haupt *et al.* in view of Anderson *et al.*, Gordan *et al.*, Luther *et al.*, and Lu *et al.* Claim 26 stands rejected over the same references as claim 1 and further in view of Bennet *et al.* Claim 28 stands rejected over the same references as claim 1 and further in view of Tanabe *et al.* Claim 53 stands rejected over the same references as claim 1 and further in view of Bennett *et al.* and Tanabe *et al.* These rejections are unwarranted.

A *prima facie* case for obviousness requires that the combination of applied references teach or suggest all limitations of the claims. *In re Royka*, 180 USPQ 580, 583 (CCPA 1974) (Obviousness requires a suggestion of all limitations in a claim). As such, all words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). Secondly, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ 1016, 1023 (C.C.P.A. 1970). Neither of these requirements has been met here.

A. The applied Combination of References Does Not Teach or Suggest all Limitations of the Claims.

Claim 1 relates to an oral DNA vaccine suitable for eliciting an immune response

against cancer cells in a patient comprising a DNA construct operably encoding at least one survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut, wherein the DNA vaccine induces a cytotoxic T-lymphocyte immune response against tumor cells when orally administered to the patient, and the attenuated *Salmonella typhimurium* vector comprises an aroA $^-$, dam $^-$ *Salmonella typhimurium* strain.

None of the applied references teaches or suggests the use of an aroA $^-$, dam $^-$ *Salmonella typhimurium* strain as a vector for a vaccine against tumor antigens. The present application (see e.g., pg. 41, lines 3-9) indicates that the an aroA $^-$, dam $^-$ *Salmonella typhimurium* strain has significant advantages over a *Salmonella typhimurium* strain that is simply an aroA $^-$, such as the strains described by Lu *et al.* Thus, the combined references do not teach or suggest all of the limitations of the present claims. Furthermore, the advantages of the an aroA $^-$, dam $^-$ strain would not have been predictable from the applied art.

B. Reasonable Expectation of Success is Lacking.

The primary reference, Haupt *et al.*, teaches that vaccinations against tumor-associated antigens is unpredictable, and that it is undesirable to directly target a single tumor-associated antigen, as in the present claims. Haupt *et al.* clearly would have suggested to one of ordinary skill in the art to target more than one antigen in order to avoid the difficulties noted in the prior art, which is contrary to the claimed invention. A reference must be considered for all that it teaches, not just that which might support a finding of obviousness. The present Office Action does not follow this admonition. The Office Action does not explain why one of ordinary skill in the art would have ignored the teachings of Haupt *et al.* regarding the inadvisability of targeting a single syngeneic antigen, while following other portions of the reference.

Additionally, the present invention does not represent a *predictable* variation of known elements or techniques in prior fields of endeavor. For *prima facie* obviousness, there must be a reasonable expectation of success that the proposed combination will work. This presupposes that the skilled person is capable of rationally predicting, on the basis of existing knowledge, the successful conclusion of the subject invention without undue experimentation. The more

unexplored a technical field of research is, the more difficult it is to make predictions about the likelihood of success. Haupt *et al.* clearly indicate that such reasonable predictions would not have been possible in the field of vaccines against tumor-associated antigens at the time of the invention due to the unpredictability of overcoming the heterogeneity of tumor antigen presentation. This is particularly true in the present case, where the claimed vaccine differs in all material aspects from the vaccines described in the primary reference (Haupt *et al.*), i.e., the claimed vaccine is targeted to a different antigen, includes a materially different vector than those described by Haupt, and the claimed vaccine incorporates DNA of a different cytokine adjuvant than the vaccines described by Haupt *et al.*

For example, Haupt indicates that "the benefit of the cytokine gene might depend on the intrinsic properties of the antigen used and the immunologic cell types used" (see page 230, col. 2, 1st par.). Haupt *et al.* discuss a number of such cytokines, but not CCL21. The article by Luther *et al.*, provides a mechanistic investigation of the effect of CCL21 cytokine in recruitment of dendritic cells and T cells. The last paragraph of the Luther *et al.* article indicates that introduction of CCL21 *into tumor cells* caused increased infiltration by dendritic cells, T cells, and in some cases granulocytes. In substituting CCL21 for the cytokines discussed by Haupt *et al.*, the Examiner appears to presume that the CCL21 will be incorporated into the tumor cells with the present vaccine. However, there does not appear to be any basis for that presumption in the case of vaccines incorporated into the claimed attenuated *S. typhimurium* vector, which targets Peyer's patches in the gut, not the tumor itself as described by Luther. Thus, one of ordinary skill in the art would not have been able to predict how CCL21 would affect vaccination with the vector of the present claims, based on the teachings of Luther *et al.* combined with Haupt *et al.*

C. No Motivation to Modify the Haupt Vaccine as Suggested.

A *prima facie* case for obviousness requires that there be a motivation for one of ordinary skill in the art to make the proposed modification of the prior art. MPEP 2143.01, subsection VI, states that there is no motivation to combine references where the proposed modification or combination would change the principle of operation of the prior art invention being modified. See *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (1959). In the *Ratti* case, the

invention was an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in the rejection disclosed an oil seal wherein the bore engaging the portion was reinforced by a cylindrical sheet metal casing. The prior art patentee taught the device required rigidity for operation, whereas the claimed invention required rigidity. The court reversed the rejection because the suggested combination of references would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the principle under which the primary reference device was designed to operate.

In the present case, redesigning the prior art anti-tumor vaccines to incorporate a CCL21 cytokine in the claimed attenuated *S. typhimurium* vector would change the principle of operation of the cytokine enhancement from that described by Luther *et al.* (i.e., changing from Luther's direct incorporation of the cytokine *in tumor cells* to the mechanism of the claimed invention, which involves modification of antigen presenting cells found in the Peyer's patches). Consequently, the applied references would not have provided the necessary motivation to incorporate a CCL21 gene into the claimed attenuated *S. typhimurium* vector under the doctrine of *In re Ratti*.

D. The Proposed Modification is Not Obvious to Try.

The present rejections amount to nothing more than an assertion that it would have been "obvious to try" the claimed combination in view of the isolated prior art teachings of the various elements of the claims. The "obvious to try" standard, however is not applicable to the present claims, since the number of alternatives in the case of anti-tumor vaccines (choice of potential antigens, number of antigens to target, combined with choice of cytokine and choice of vector) would have been very large, and the results would not have been predictable. A finding of obviousness requires that the prior art provide a rational reason or motivation for one of ordinary skill to have combined the references. The decision of the Board in *Ex parte Kubin*, 83 USPQ2d 1410, 1414 (B.P.A.I. 2007), citing *KSR* 82 USPQ2d at 1397is informative in this respect:

> Where there is motivation to solve a problem and there are a finite number of

> identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

The Federal Circuit has recently further clarified the "obvious to try" standard in *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*, 91 USPQ2d 1569, 1572-1573 (Fed. Cir. 2009). The *Bayer* court discussed *KSR* and an earlier Federal Circuit decision , *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988), and noted:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *Bayer* 91 USPQ2d at 1572-1573 (citations omitted).

The *Bayer* court reiterated the admonition of *O'Farrell* that an invention is not obvious to try where:

> vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Bayer* 91 USPQ2d at 1573 (citations omitted).

The present rejection falls squarely within the factual framework of situations which the *O'Farrell* and *Bayer* courts have indicated are *not* obvious to try. Accordingly, withdrawal of the present obviousness rejections is warranted. The Office Action emphasizes that survivin is one of only four alleged "universal" tumor-associated antigens, implying a finite number of choices. Haupt *et al.*, on the other hand, highlight the unpredictable nature of vaccines targeting tumor-associated antigens, and point to many at least partially successful strategies for anti-tumor vaccines besides targeting "universal" antigens. Consequently, the number of potential antigen targets available to one of ordinary skill in the art at the time of the invention was much larger than just the four so-called "universal antigens" alluded to in the Office Action.

In addition, the claims are not directed only to the antigen DNA, but rather to a *combination* of antigen DNA, cytokine DNA, and a specific vector. The prior art discloses numerous vectors, numerous cytokine, and numerous tumor antigen target from which to choose. A selection for each these variables is required to prepare the claimed vector based on the applied art. Clearly, there are, in fact, a very large number of potential combinations for the tumor antigen, the cytokine adjuvant, and the delivery vehicle that will be effective for both the tumor antigen and the cytokine. The evaluation of each of these combinations clearly would have involved undue experimentation, since the person of ordinary skill in the art would have needed "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result" (see *Bayer* USPQ2d at 1573). See also *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (no identification of a predictable solution where prior art discloses a *broad selection of compounds*).

The applied prior art provides many alternaitve strategies for preparing an anti-tumor DNA vaccine (see e.g., Haupt *et al.*, which provides a review of several strategies, and Gordan *et al.* which presents the concept of targeting "universal' antigens). Given the unpredictable nature of anti-tumor vaccines, and the fact that the prior art provides many options for tumor antigen targets, cytokines, and vectors, it is clear that the prior art would not have "[guided] an inventor toward a particular solution", much less the claimed solution (see *Bayer* USPQ2d at 1573). The only clear guidance of record for the selection of the claimed elements is provided in the present

specification, which cannot properly be used in hindsight for such selection.

Conclusion.

In view of the foregoing, Applicants request reconsideration, allowance of the present claims, and early passage of the application to issue. In the event the foregoing is not deemed to be persuasive, Applicants request entry of the present amendment to place the claims in better form for appeal,

Respectfully submitted,

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